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Alveolar Rhabdomyosarcoma of the Lip in an Infant

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Anthony V. D'Amico, MD (Radiation Oncology Fellow)

The patient is an 8-month-old male who was noted by his parents at the age of 2 weeks to have a 0.5 × 0.3 cm smooth, mobile, soft tissue mass on the mid-left upper lip parallel to the filtrum. The child was seen when 5 months old by a pediatric plastic surgeon at the local hospital. The working diagnosis at that time was juvenile xanthogranuloma or a dermoid cyst. The plan was to follow closely and reevaluate at 1 year of age or sooner if there was growth or change in the characteristics of the mass. Rapid growth did, in fact, ensue, dimensions becoming 0.8 × 0.4 cm in 6 weeks. Because of the rapid growth, an excisional biopsy was performed and reported as a small round cell tumor consistent with an alveolar rhabdomyosarcoma. The margins of the resected specimen contained tumor cells, and several days after the initial excisional biopsy, he rapidly developed bilateral level one cervical lymphadenopathy measuring 1.5 × 1.0 cm on the left, and 2.0 cm × 1.5 cm on the right. A reexcision of the primary site showed no residual tumor, and fine-needle aspirations of both neck masses confirmed metastatic rhabdomyosarcoma.

Positive findings on staging work-up included a healing surgical left lip wound and the presence of bilateral cervical adenopathy. CBC and chemistries were normal except for an LDH elevated to 849. Chest x-ray films, CT scans of the thorax and abdomen, bone scan, and bilateral posterior iliac crest bone marrow aspirations and biopsies, all were within normal limits. MRI of the head and neck showed bilateral 2 × 2 × 2 cm cervical masses in the left parotid and right submandibular areas.

The child was seen at a major pediatric cancer center, was considered to have Stage I, Group III disease, and was started on triple-drug chemotherapy (VAC = vincristine, dactinomycin, and cyclophosphamide). There was a complete clinical response to the first cycle of VAC, after which radiation therapy was planned.

The parents come here for an opinion concerning the radiation therapy to be given and future management in general.

On physical examination, M.O. is an active 8-month-old infant weighing 12 lbs., and 21 cm. in length, who is alert and appropriately responsive. There was a well-healed mid-upper-left lip incision with no signs of recurrent disease. There is no palpable adenopathy in the submandibular, or cervical, or supraclavicular regions. A long-line catheter is in place in the right antecubital fossa with no signs of local induration. There are no other findings on physical examination.

Joel Goldwein, MD (Pediatric Radiation Oncologist)

Dr. D'Amico, you have reviewed the literature concerning what has been done radiotherapeutically in patients like this. Could you summarize what you have learned for us?

Dr. D'Amico. A review of the first Intergroup Rhabdomyosarcoma Study (IRS-I) [1] revealed that of 57 patients with non-parameningeal head and neck rhabdomyosarcoma (RMS), the 3-year disease-free survival was 75%. However, 70% of these patients had embryonal histology and only 10% had alveolar histology. A subsequent study by Hays et al. [2] of Group III and IV alveolar RMS patients evaluated the rates of complete response, relapse after complete response, and patterns of failure. The investigators found that for Group III alveolar histology patients, there was an increased relapse rate after complete response to induction chemotherapy, as

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well as increased mortality and more regional failures as compared to their embryonal histology counterparts. These data indicate that the alveolar subtype portends a worse prognosis.

Regarding local control as a function of radiation therapy dose for Group III patients, data are available from IRS-I [3], Princess Margaret Hospital [4], and the M.D. Anderson [5], and Memorial Sloan-Kettering cancer centers [6]. The IRS series shows no dose response for doses above or below 50 Gy with 89 and 86% local control, respectively. However, the Princess Margaret Hospital shows a dose response relationship with a local control of 62% for doses between 45 and 50 Gy, 73% for doses 50 to 55 Gy, and 100% for doses greater than or equal to 55 Gy. The M.D. Anderson center only reports for doses greater than or equal to 55 Gy, when 85% local control is achieved. Finally, Memorial notes that 50% local control was achieved in Group III patients after less than 45 Gy. A rate of 67% is reported for doses of 50–55 Gy, and 92% for more than 55 Gy. Based on these data, the current standard schedule for Group III patients in IRS-IV is 50.4 Gy. This is currently being compared to 59.4 Gy given with a hyperfractionated schedule of 1.1 Gy b.i.d..

Recent data from Agine et al. [7] provide additional insight. They reviewed 109 patients, 28 of whom had the disease burden decreased to microscopic residua after chemotherapy plus or minus surgery. These patients then received radiation therapy at doses ranging from 14 to 51.5 Gy with a mean of 40.35 Gy. With a minimum follow-up of 2 years, they found an overall local control rate of 82%. The local control was 50% if the dose was less than 40 Gy but 91% if the dose was greater or equal to 40 Gy. This difference was significant at the $P = .02$ level. They therefore suggest that doses as low as 40 Gy may be sufficient for Group III patients whose disease is reduced to microscopic residua after chemotherapy plus or minus surgery.

One could use radiobiologic principles to calculate the hyperfractionated dose needed to approximate the results reported for 40 Gy delivered in once-a-day fractionation. The goal of such a hyperfractionated regimen would be to achieve equivalent tumor control with a decrease in the late complications in normal tissues. Using the alpha-beta model with an alpha over beta equal to 10 for tumor effect and alpha over beta equal to three for late tissue damage, one arrives at a hyperfractionated dose of 44 Gy given in 1.1 Gy b.i.d. doses. This would be equivalent to 41.4 Gy after 1.8 Gy given once a day. Therefore, this analysis would recommend the delivery of 44 Gy in 1.1 Gy b.i.d. at the end of 12 cycles of chemotherapy, or sooner, should progression during chemotherapy occur. It is important to bear in mind, however, that the dose-response data are based primarily on embryonal RMS experience. Only a small proportion of the patients had alveolar RMS, so that these data do not necessarily apply to this child.

Audrey E. Evans, MD (Pediatric Oncologist)

Thank you for a very thorough review of the literature. There would seem to be scant data that will help us in deciding how best to manage this baby. It would help me to understand one of the options better if you could tell me more about what you call "hyperfractionated radiation therapy." What is the rationale, and why is it particularly attractive in this situation?

Dr. Goldwein. Hyperfractionation provides the hope there will be an equivalent effect against the tumor with a reduction in the damage to the surrounding soft tissue using doses similar to those employed in once-a-day therapy. With a higher nominal dose such that there is an isoeffect on the normal tissues, a greater tumor cell kill is predicted.

Michael Needle, MD (Pediatric Neuro-Oncologist)

What if radiation therapy were to be delayed in this child to allow perhaps a year or so of further growth? Does that jeopardize the chance for success?

Giulio J. D'Angio, MD (Pediatric Radiation Oncologist)

Timing of radiation therapy can make a difference. Studies over many years of the delay in the initiation of radiation therapy in children with Wilms' tumor show a curious phenomenon. Delays of more than 10 days after surgery are associated with a worse outcome [8]. Clearly, that datum can't be extrapolated to this particular patient. To repeat what Dr. Evans said, there are insufficient studies in this particular situation to make an intelligent estimate.

Nancy Bunin, MD (Pediatric Oncologist)

The child had a very satisfactory response to the chemotherapy so far given. What are the chances that chemotherapy alone would suffice?

Richard Womer, MD (Pediatric Oncologist)

There are no data concerning this histology or certainly this location. There have been attempts over the years to control pelvic embryonal rhabdomyosarcoma (ERMS) with chemotherapy alone. That lesion is far more responsive to chemotherapy than its alveolar counterpart. While there are some patients who appear to have been managed satisfactorily with chemotherapy alone for many years, late recurrences are not infrequent.

Dr. Goldwein. Among the problems in giving high-dose radiation therapy to the neck in a baby like this is that it may compromise development of the vasculature. Not only would there be underdevelopment of the bone and soft tissues, but the carotids might well fail to de-

velop fully, leading to underdevelopment and relative narrowing at the level of the treatment; that is, an acquired coarctation. This might compromise normal perfusion of the brain. Secondary changes in major vessels of this kind after radiation therapy are well-known late sequel of radiation therapy. An implant would reduce the volume irradiated, but high doses would still be delivered to the vessels. This method could therefore magnify the problem; in fact, could be dangerous. In view of these difficulties, but still in the belief that radiation therapy of the neck is necessary, I would prefer to delay irradiation as long as possible.

Is there any role for surgical intervention at this point? The lip lesion appears to have been excised completely with clear margins. The neck nodes have decreased markedly; Dr. Handler, would neck dissections make sense at this point?

Steven Handler, MD (Pediatric Otolaryngologist)

I don't think so, since surgery would entail bilateral formal neck dissections without much to guide us in the short neck of an infant. Even modified dissections can result in deformity and edema of the structures of the head and neck.

Judith Margolin, MD (Pediatric Oncologist)

Would "cleaning out" the neck surgically make subsequent treatment easier, however? Would it allow one to be less aggressive radiotherapeutically, for example?

Dr. Goldwein. Perhaps, but that strategy is best applied when dealing with "bulk" disease. Chemotherapy has reduced the nodes considerably in this case, and it is possible that additional chemotherapy will lead to further reduction of the masses.

Dr. Womer. Since our radiotherapy and surgical colleagues are reluctant to intercede at this point, we should return to the potential value of chemotherapy alone. Investigators in The Netherlands have tried very aggressive chemotherapy using ifosfamide, vincristine, and dactinomycin. They have found in children with pelvic ERMS that local control with chemotherapy alone can be obtained for long periods of time. Late recurrences—as long as 8 years later—have been encountered by them, however. French investigators have tried the same approach in children with orbital rhabdomyosarcomas of the embryonal type. They have obtained complete responses, but there is a high rate of relapse. Chemotherapy alone has also been tried with ERMS of the extremities in patients in whom lymph node involvement was documented, but the result was bad. Our German colleagues have titrated the amount of radiation therapy according to the response to chemotherapy, giving 30 Gy to those who respond, and 56 Gy to those who fail to respond.

Dr. Needle. What is the difference in growth retardation and other untoward effects when one gives 40 rather than 50 Gy?

Jeffrey Silber, MD (Pediatric Oncologist)

The best estimate that can be made is how treatment affects residual growth at the age of treatment. We have done this for children with Hodgkin's disease, for example. Parts of the body that have less growth remaining will be affected less than those, like the long bones, that are marked by pronounced increases in length at relatively later ages. In the case of a head and neck lesion, the percentage of growth remaining is much less after age 3 years than in other parts; therefore, a differential between 40 and 50 Gy would be less pronounced than it might be elsewhere in the body in children older than 3 years of age.

Dr. Evans. How low a radiation therapy dose need be given before "bad" late effects are not so bad?

Dr. Goldwein. It is extremely difficult to arrive at specific doses that are more than informed guesses. It would depend on what is meant by "bad." In a child this young, even doses as low as 200–400 cGy can result in dentition difficulties such as maleruptions and malocclusions. Higher doses are associated with profound growth and development problems.

What seems to be clear, however, is that hyperfractionation techniques are worth considering in these situations, especially in children this young for the reasons already explained.

Dr. D'Angio. Dr. Goldwein, would combined radiation therapy approaches be of value here? Though complex, would it be possible to use brachytherapy with or without electron beams as well as photon irradiation fields? Such "mixing and matching" would perhaps allow one to get doses to the lip and the lymph node regions while minimizing the effects on normal tissue.

Dr. Goldwein. Such an approach is worth considering. It does not make much sense to me, however, to deal with the lip and not the intervening lymph node drainage areas leading to the neck nodes. Any approach to such a large field in continuity adds to the complexities of any treatment plan. I would assume that the lip lesion has been controlled by the surgery performed along with the chemotherapy, and focus on control of the residual disease in the neck.

Dr. D'Angio. One thought that came to mind is the possible addition of hyperbaric oxygenation (HBO) during the time brachytherapy sources were in place. Dr. Voûte and his colleagues in Amsterdam have used that approach in children with neuroblastoma who receive radioactive metaiodobenzylguanidine (MIBG). Dr. Goldwein, do you think such an approach might get you a greater tumor cell kill for the prescribed dose?

Dr. Goldwein. There might be an advantage on radio-

biological grounds, but the logistics and complexities of having a baby in the chamber are daunting. The number of "dives"; that is, HBO exposures, would necessarily be limited.

My choice would be to continue with chemotherapy until his current chemotherapy courses are complete, which means for about an additional year.

Dr. D'Angio. I would agree with that, and perhaps extend it even further. He has had a dramatic response to the chemotherapy. It might be worth waiting after the completion of chemotherapy to see what develops. Obviously, very careful follow-up would be needed. If this baby's course were like the children with ERMS managed with chemotherapy alone, the relapse might be put off for many years. This would have all the advantages that have been brought out in the discussion up to this point. If he relapsed in the lung, let alone the neck, clearly a shift in chemotherapy would be necessary, and there are agents that have given reasonably good responses under that set of circumstances. It also is obvious that chemotherapy would have to be supplemented with surgical excisions and radiation therapy or any mixture of the three elements depending on what the clinical course dictated.

When I don't know what best to do—and I certainly do not know what is best for this child—I enlist the help of the child in helping me decide. It is difficult to know how aggressive one should be with surgery and radiation therapy at this point because of the excellent chemotherapy response. I would prefer to have the disease declare itself again in this child, and then deal with it vigorously at that point, the need to be aggressive having been made obvious by the recurrence.

Dr. Needle. There is some precedent for this in babies with medulloblastoma where chemotherapy has delayed or eliminated the use of irradiation. The decision to use radiation therapy is made at the end of chemotherapy when the child is several months older.

Dr. Womer. The decision is extremely difficult, we can all agree. Let me summarize what seems to be the prevailing opinion. We propose that chemotherapy using VAC be continued until the current course is complete. Radiation therapy would then be added in whatever way the responsible radiation oncologist thinks to minimize the late effects. If and when the child relapses, using a combination of etoposide and ifosfamide with surgery and radiation therapy as thought indicated then would be our recommendation.

Dr. D'Amico. Three leading pediatric radiation oncologists were consulted by the parents. One believed full-dose radiation therapy should be given to all implicated areas. The second advocated interstitial radiation therapy of the neck. The third preferred a b.i.d. approach; that is, a hyperfractionated method. A total dose of about 40 Gy would be delivered in this manner. The preference was based on some promising preliminary results using this technique in ERMS patients.

ADDENDUM

The child returned to his home institution where an MRI of the head and neck was performed after the completion of three cycles of VAC chemotherapy. It showed the presence of bilateral 1.5 cm submandibular lymph nodes, and surgical exploration of the neck removed seven lymph nodes. Four (two right, two left) were involved with metastatic RMS but none had evidence of extracapsular extension. After considerable discussion, it was decided to proceed with radiation therapy post-operatively. A total dose of 5,225 cGy was given (4,180 cGy to the 80% isodose line) using electrons of 16 MeV and 9 MeV. An additional 10 cycles of VAC was delivered (omitting dactinomycin during irradiation), and the child remains free of disease 4 months off therapy.

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SERIES EDITOR'S NOTE

The *-baryc* in "hyperbaric" derives from the Greek *barys* meaning "heavy" and by extension, "pressure." It appears in several words in science; e.g., *barometer* and *barium*, the element that was discovered by Scheele in 1779. Barium was isolated from a mineral named *baryta* because of its weight. Another word derived from *barys* is *baryon*, a nucleon that is one of the elementary particles believed to be combinations of 3 *quarks*. "Quark" holds considerable interest. According to Ayto,[1]

> "The term *quark* was applied to a type of fundamental particle by its discoverer, the American physicist Murray Gell-Mann. He seems first to have used *quork*, but then he remembered *quark*, a nonsense word used by James Joyce in "Finnegan's Wake" in 1939, and he decided to plump for that. It first appeared in print in 1964."

It would seem that Joyce did not coin the word, either. Rather, he apparently subsumed (Latin: *sub-* + sumere = take up) the word from the German where it is applied to a form of cheese. "Quark" in German also appears to have scatalogical (Greek: *skor* = excrement; dung, which is from old Norse *dyngja* = manure pile) connotations. Some Joycean scholars believe it was this latter meaning he had in mind. It also is used by the Germans to mean "trivial nonsense," which is hardly true of Dr. Gell-Mann's epochal discovery. Trivial is from the Latin *tri-* + via = three ways (roads), or a crossroads, which is where people meet to exchange unimportant small talk or gossip. Be that as it may, physicists seem to delight in using casual words like "charm" or "barn" in discussing some of their concepts, arcane [(Latin: hidden or secret from *arca* (chest or box)] to ordinary mortals.

Finally, *gossip* deserves some comment. It derives from the old English *godsibb* (God + sibb [kinsman]), and meant a person related through God; i.e., a godparent or godchild. It explains its appearance in Shakespearean plays where an old person, usually a woman, was addressed as "good gossip". Here the meaning is not restrictive, but is more akin to "my good woman." Old folk of either sex are fond of exchanging stories and news, so the term was applied first to persons engaged in such talk and then to the talk itself.

[1]Ayto J: "Dictionary of Word Origins." New York: Arcade Publishing, 1991.